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An Aminopyridinato Titanium Catalyst for the Intramolecular Hydroaminoalkylation of Secondary Aminoalkenes

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Dedicated to Professor Stephen L. Buchwald on the occasion of his 60th birthday.

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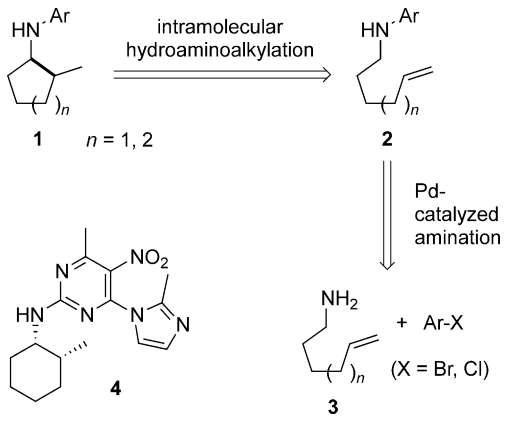
Abstract: The easily accessible 2-(methylamino)pyridinato titanium complex initially synthesized by Kempe is used as catalyst for efficient intramolecular hydroaminoalkylation reactions of secondary aminoalkenes. The corresponding reactions of *N*-aryl-substituted 1-aminohept-6-enes and 1-aminohex-5-enes directly give access to 2-methylcyclohexyl- or 2-methylcyclopentylamines in good yields. In addition, intramolecular hydroaminoalkylations of an *N*-alkyl-substituted secondary aminoalkene and a geminally β-disubstituted substrate are described for the first time. While all products are formed as mixtures of two diastereoisomers, better *trans*/*cis* ratios are observed during the formation of 2-methylcylopentylamines.

Keywords: alkylation; amines; C–H activation; hydroaminoalkylation; titanium

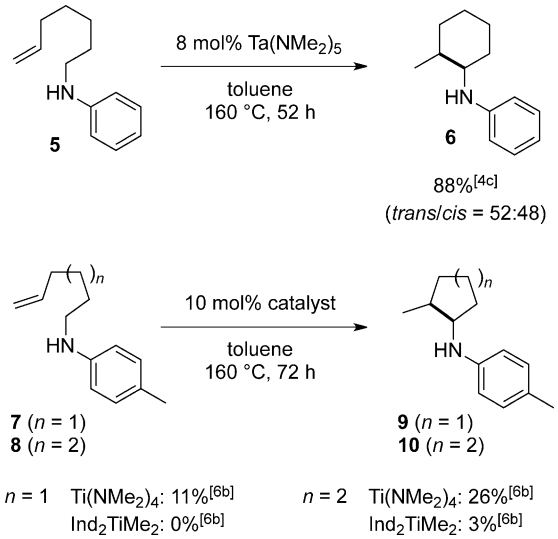
Introduction

Owing to the great importance of amines in the agrochemical, fine chemical and pharmaceutical industries, the development of efficient synthetic methods for the production of amines has become a research area of general importance. Among the various synthetic strategies for the synthesis and transformation of nitrogen-containing molecules, metal-catalyzed C–H bond activation that can be achieved selectively in the α-position to a nitrogen atom deserves particular attention. For example, the so-called hydroaminoalkylation of alkenes[1] which takes place by direct addition of α-C(sp^3)–H bonds of primary or secondary amines across C=C double bonds offers a 100% atom economic conversion of readily available amine and alkene feedstocks into more complex α-alkylated amines. Although a variety of ruthenium,[2] iridium,[3] group 5 metal,[4] zirconium,[5] and titanium complexes[6] were found to catalyze hydroaminoalkylation reactions of alkenes, a number of limitations still exist. For example, intermolecular transformations can only be achieved with secondary amine substrates and best results are obtained with *N*-arylated alkylamines. On the other hand, intramolecular hydroaminoalkylation reactions of primary aminoalkenes[5,6a–c,e,j] generally proceed more smoothly than the corresponding reactions of secondary aminoalkenes.[4c,6b,c] Especially the latter transformations have rarely been described in the literature and in all these cases, only *N*-aryl-substituted aminoalkenes of type **2** (Scheme 1) were used.

Intramolecular hydroaminoalkylation of secondary *N*-aryl-substituted aminoalkenes of type **2** which are



Scheme 1. Intramolecular hydroaminoalkylation as a key step of the retrosynthetic analysis of 2-substituted cycloalkylamines and structure of the cytomegalovirus inhibitor **4**.



Scheme 2. Intramolecular hydroaminoalkylation of secondary aminoalkenes performed with tantalum or titanium catalysts.[4c,6b]

easily accessible by reductive amination of alkenals with anilines or by palladium-catalyzed Buchwald–Hartwig amination of aryl halides with corresponding primary aminoalkenes **3**[7] directly gives access to 2-substituted secondary cycloalkylamines **1** which are common subunits of biologically active compounds. For example, the 2-substituted cyclohexylamine moiety present in the cytomegalovirus inhibitor **4**[8] is regarded as a privileged and frequently occurring motif in drug design.[9] So far successful intramolecular hydroaminoalkylation of secondary aminoalkenes has only been reported with substrates **5**, **7** and **8** (Scheme 2) using $Ta(NMe_2)_5$,[4c] $Ti(NMe_2)_4$,[6b] $TiBn_4$,[6c] or Ind_2TiMe_2[6b] (Ind = η^5-indenyl) as the catalysts. Among these catalysts, only $Ta(NMe_2)_5$ gave a good yield of the corresponding cyclization product **6** (88%) but unfortunately, the *cis*- and the *trans*-diastereoisomers of **6** were formed in a ratio close to 1:1.[4c] On the other hand, all titanium-based catalysts showed poor activity and, as a result, only disappointing yields of the hydroaminoalkylation products **9** and **10** ($\leq$26%) could be obtained.[6b,c] Besides the harsh reaction conditions reported for all intramolecular hydroaminoalkylation reactions of the secondary aminoalkenes **5**, **7** and **8**, an additional problem is that the catalyst Ind_2TiMe_2 was found to isomerize the double bond of similar geminally disubstituted aminoalkenes which results in the formation of aminoalkenes with internal alkene moieties.[6d]

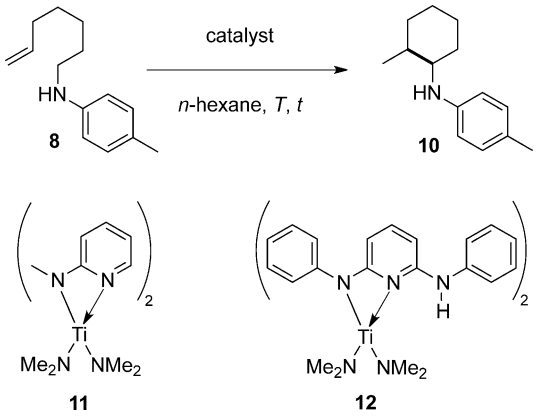
Herein, we present the first example of a titanium-based complex that catalyzes high-yielding intramolecular hydroaminoalkylation reactions of various secondary aminoalkenes and its use for the synthesis of 2-methylcyclohexyl- and 2-methylcyclopentylamines.

Results and Discussion

Due to the broad scope of titanium catalysts for the intermolecular hydroaminoalkylation of alkenes with *N*-arylated alkylamines and especially the recent improvements achieved with aminopyridinato titanium catalysts **11**,[6g] initially synthesized by Kempe,[10] and **12**,[6i] we decided to start a reinvestigation of the intramolecular hydroaminoalkylation of secondary aminoalkene **8** using **11** and **12** as the catalysts (Table 1). For that purpose, we initially performed a control cyclization of **8** at 140 °C in *n*-hexane (sealed Schlenk tube) in the presence of 10 mol% of the catalyst $Ti(NMe_2)_4$ which gave cyclohexylamine **10** in 21% yield with a *trans*/*cis* ratio of 75:25 (Table 1, entry 1). This result is in good agreement with earlier findings that have already been presented in the literature.[6b,c]

In contrast to the poor performance of $Ti(NMe_2)_4$, we observed a distinct increase in yield with the 2-(methylamino)pyridinato titanium catalyst **11** which is easily accessible from $Ti(NMe_2)_4$ and 2 equivalents of

Table 1. Brief optimization of the intramolecular hydroaminoalkylation of secondary aminoalkene **8**.



Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	Yield [%][a]	Selectivity *trans*/*cis*[b]
1	$Ti(NMe_2)_4$ (10)	140	96	21	75:25
2	**11** (10)	140	96	97	55:45
3	**12** (10)	140	96	11	62:38
4	**11** (10)	140	24	96	56:44
5	**11** (10)	140	16	97	55:45
6	**11** (10)	120	96	93	56:44
7	**11** (10)	100	96	27	55:45
8	**11** (10)	50	96	–	–
9	**11** (5)	140	96	97	54:46
10	**11** (5)	140	24	97	54:46
11	**11** (5)	120	96	85	52:48

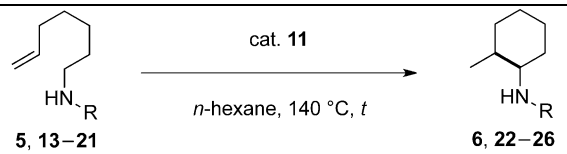
[a] *Reaction conditions:* aminoalkene **8** (2.0 mmol, 407 mg), catalyst (5 mol% or 10 mol%), *n*-hexane (2 mL), *T*, *t*. Yields refer to the total yield of isolated product (*trans* + *cis*).

[b] GC analysis prior to chromatography.

commercially available 2-(methylamino)pyridine.[10] After heating a solution of aminoalkene **8** and 10 mol% of **11** in *n*-hexane to 140 °C for 96 h it was possible to isolate the hydroaminoalkylation product **10** in almost quantitative yield (97%, Table 1, entry 2). However, it must be noted that the diastereoselectivity of the reaction which still slightly favors formation of the *trans*-diastereoisomer decreased to a *trans*/*cis* ratio of 55:45. In contrast to this very promising result, the 2,6-bis(phenylamino)pyridinato titanium catalyst **12** gave a disappointing yield of only 11% under identical conditions (Table 1, entry 3), a result that is even worse than that obtained with $Ti(NMe_2)_4$. A comparison of the results of Table 1, entries 1–3 clearly supports the assumption that the aminopyridinato ligands remain bonded to the titanium center during the course of the reaction because otherwise comparable yields and diastereoselectivities would be expected with the catalysts $Ti(NMe_2)_4$, **11** and **12**. Inspired by the promising result obtained with **11**, we then performed a brief optimization study with this catalyst (Table 1, entries 4–12). First of all, it was noticed that stirring the reaction mixture at 140 °C overnight (16–24 h) is sufficient for this reaction to reach 100% conversion and correspondingly high yields of 96% and 97% were obtained in these cases (Table 1, entries 4 and 5). On the other hand, the reaction temperature was found to influence the outcome of the reaction significantly. While a slightly reduced temperature of 120 °C only led to a slight drop in yield (93%, Table 1, entry 6), the yield decreased dramatically to 27% at 100 °C (Table 1, entry 7) and finally, it turned out that the reaction does not proceed at all at 50 °C (Table 1, entry 8). Additional attempts to reduce the catalyst loading (Table 1, entries 9–11) then revealed that cyclohexylamine **10** is still formed in 97% yield at 140 °C with a catalyst loading of only 5 mol% of **11** and even in this case, a reaction time of only 24 h is sufficient to reach 100% conversion of aminoalkene **8** (Table 1, entries 9 and 10). On the other hand, with the same catalyst loading, the reaction did not go to completion within 96 h at 120 °C and under these conditions, product **10** was only isolated in 85% yield (Table 1, entry 11). As can be seen from Table 1, entries 3–11, the diastereoselectivity of the hydroaminoalkylation of **8** catalyzed by aminopyridinato complex **11** was not significantly influenced by the reaction time, the reaction temperature or the catalyst loading and as a result, the *trans*- and the *cis*-isomers of **10** were always formed in a ratio close to 1:1 with this catalyst. However, a comparison of the diastereoselectivities obtained with the catalysts $Ti(NMe_2)_4$, **11** and **12** (Table 1, entries 1–3) leads to the impression that a future optimization of the diastereoselectivity of the reaction might be possibly by varying the ligands bound to the titanium center.

Encouraged by the high catalytic activity of complex **11** with aminoalkene **8**, we then studied the substrate scope of the intramolecular hydroaminoalkylation using a variety of further functionalized secondary 1-aminohept-6-enes (Table 2). For that purpose, we initially chose the optimized conditions of Table 1, entry 10 (5 mol% **11**, 140 °C, 24 h) but unfortunately, we recognized that several reactions do not go to completion within 24 h and often significantly improved yields were obtained with a catalyst loading of 10 mol%. For example, cyclization of the simple *N*-phenyl-substituted aminoalkene **5** (Table 2, entries 1 and 2) gave the corresponding 2-methylcyclohexylamine **6** in 43% yield after 24 h while a yield of 95% was obtained after 96 h. Although the sterically demanding *ortho*-methyl-substituted aminoalkene **13** did not react at all under the applied conditions (Table 2, entries 3 and 4), the corresponding *meta*-methyl-substituted substrate **14** could be converted successfully to cyclohexylamine **22** (Table 2, entries 5 and 6). Interestingly, in this case a catalyst loading of 10 mol% and a reaction time of 96 h were necessary to achieve a yield of 94%. The fact that the corresponding *para*-methyl-substituted analogue **8** had already turned out to be far more reactive than **14** (see Table 1, entry 10) and the observed lack of reactivity of the *ortho*-methyl-substituted substrate **13** suggest that catalyst **11** is very sensitive to steric hindrance close to the nitrogen atom of the aminoalkene. This observation is consistent with the proposed theory that the efficiencies of titanium-catalyzed intermolecular hydroaminoalkylation reactions of alkenes are strongly influenced by the steric bulk of the amine.[6b,d,i,k] On the other hand, the diastereoselectivity of the cyclization reaction does not seem to be influenced significantly by the presence of methyl substituents in the *meta*- or *para*-position of the phenyl substituent and as a result, the products **6**, **10** and **22** were obtained with almost identical *trans*/*cis* ratios ranging from 52:48 to 56:44. Additional reactions with the *N*-phenylaminoalkenes **15**–**18** (Table 2, entries 7–12) then revealed that the nature of the substituent on the benzene ring of the aminoalkene seems to influence the efficiency of the reaction significantly. For example, aminoalkene **15** bearing an electron-donating *para*-methoxy-substituent on the benzene ring gave the hydroaminoalkylation product **23** in 81% yield (Table 2, entry 8, 10 mol% **11**) while the corresponding substrate **16** with the strongly electron-withdrawing *para*-trifluoromethyl substituent did not react successfully (Table 2, entries 9 and 10). The latter result is in good agreement with the established fact that *N*-methyl-*para*-trifluoromethylaniline has already been identified as a poor substrate for intermolecular titanium- or tantalum-catalyzed hydroaminoalkylation reactions.[4m,6d,h] In this context, it is worth mentioning that aminoalkene **16** is not consumed under the reaction

Table 2. Formation of 2-methylcyclohexylamines by intramolecular hydroaminoalkylation of secondary 1-aminohept-6-enes.



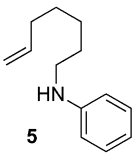
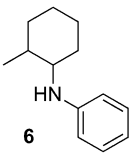
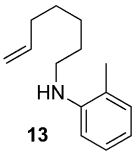
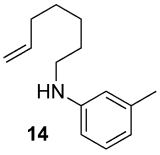
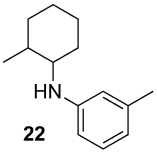
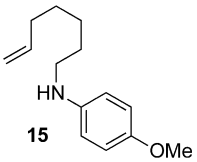
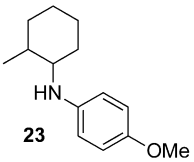
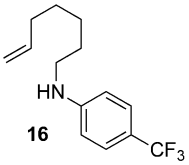
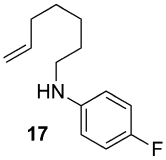
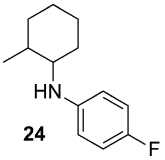
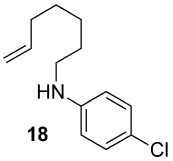
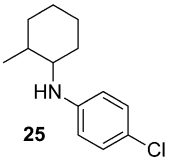
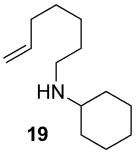
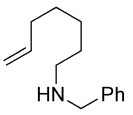
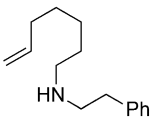
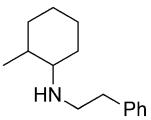
Entry	Aminoalkene	11 [mol%]	t [h]	Product	Yield [%][a]	Selectivity trans/cis[b]
1	 5	5	24	 6	43	55:45
2		5	96		95	54:46
3	 13	5	96	–	–	–
4		10	96	–	–	–
5	 14	5	96	 22	37	53:47
6		10	96		94	56:44
7	 15 OMe	5	96	 23 OMe	15	27:73
8		10	96		81	27:73
9	 16 CF_3	5	96	–	–	–
10		10	96	–	–	–
11	 17 F	10	96	 24 F	39	53:47
12	 18 Cl	10	96	 25 Cl	52	51:49
13	 19	10	96	–	–	–

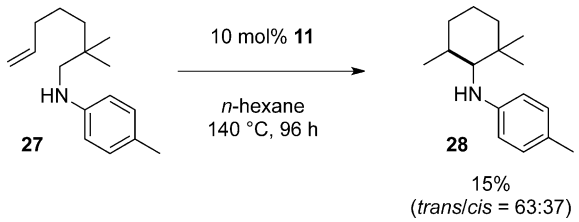
Table 2. (Continued)

Entry	Aminoalkene	**11** [mol%]	*t* [h]	Product	Yield [%][a]	Selectivity *trans*/*cis*[b]
14	 **20**	10	96	—	—	—
15	 **21**	10	96	 **26**	30[c]	1:1[d]

[a] *Reaction conditions:* aminoalkene (2.0 mmol), **11** (35 mg, 0.1 mmol, 5 mol% or 70 mg, 0.2 mmol, 10 mol%), *n*-hexane (2 mL), 140 °C, *t*. Yields refer to the total yield of isolated product (*trans* + *cis*).
[b] GC analysis prior to chromatography.
[c] The reaction was performed at 180 °C.
[d] Ratio of diastereoisomers determined by ^{1}H NMR after chromatography.

conditions and as a result, no formation of any additional products could be observed. Interestingly, the presence of the *para*-methoxy group in **15** also caused a significantly improved diastereoselectivity of the reaction in favor of the *cis*-diastereoisomer of **23** (*trans*/*cis* = 27:73), a behavior which was not observed with the *para*-fluoro- or *para*-chloro-substituted aminoalkenes **17** and **18**. In the latter two cases, the *cis*- and the *trans*-diastereoisomers of the products **24** and **25** were again formed in ratios close to 1:1 (Table 2, entries 11 and 12) and, in addition, only modest yields of 39% and 52%, respectively were obtained. The already observed trend that in comparison to arylalkylamines, dialkylamines are generally less reactive substrates for titanium- and tantalum-catalyzed intermolecular hydroaminoalkylation reactions with alkenes[1c,4,6] was then strongly underlined by the lack of reactivity of the *N*-cylohexyl- and *N*-benzyl-substituted aminoalkenes **19** and **20** (Table 2, entries 13 and 14). Both substrates did not undergo any reaction under the applied conditions. However, finally, we were delighted to recognize that catalyst **11** is able to convert the *N*-(2-phenylethyl)-substituted aminoalkene **21** into cyclohexylamine **26** if the reaction was performed at 180 °C. Although the obtained yield (30%) and the diastereoselectivity (*trans*/*cis* = 1:1) were only modest, to the best of our knowledge, this reaction represents the first example of an intramolecular metal-catalyzed hydroaminoalkylation of an *N*-alkyl-substituted secondary aminoalkene.

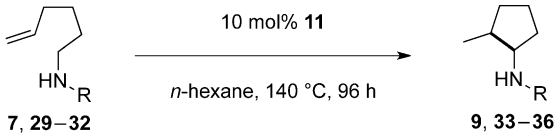
Impressed by the unique reactivity of catalyst **11**, we also tried to convert the sterically hindered geminally β-disubstituted 1-aminohept-6-ene **27** into cyclohexylamine **28** (Scheme 3). In this context, it must be noted that, so far, corresponding reactions have always failed in the presence of titanium catalysts.[6b,d,j] For example, with Ind_2TiMe_2 as the catalyst, instead of a hydroaminoalkylation reaction of **27**, an isomerization of the C=C double bond, which is probably caused by a competing C–H bond activation in the sterically less hindered allylic position, occurs.[6d] However, using 10 mol% of catalyst **11**, it was possible to achieve a successful hydroaminoalkylation of substrate **27** at 140 °C which delivered the corresponding product **28** as a mixture of two diastereoisomers in a *trans*/*cis* ratio of 63:37. Although the yield of 15% was only modest and a comparable result was obtained at 180 °C, to the best of our knowledge, this is the first example of a successful intramolecular hydroaminoalkyation of a geminally disubstituted secondary aminoalkene and correspondingly, this result can be regarded as the starting point for further optimization studies.

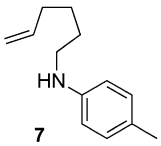
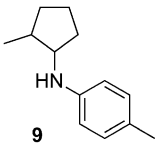
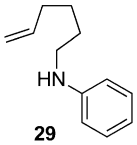
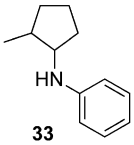
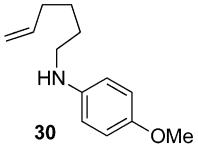
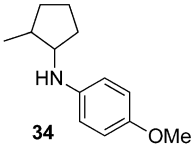
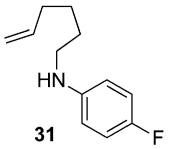
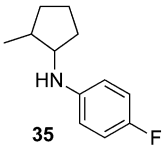
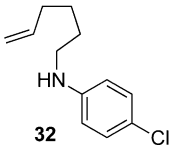
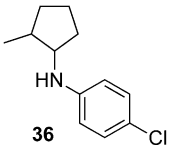


Scheme 3. Intramolecular hydroaminoalkylation of a β-disubstituted secondary 1-aminohept-6-ene.

After additional attempts to synthesize the cyclopentylamine **33** from secondary 1-aminohex-5-ene **29** (Table 3, entry 2), which were initially performed in the presence of 5 mol% of catalyst **11** and/or with a reaction time of 24 h, gave the desired product **33** only in low yields (19–22%), we decided to run all further

Table 3. Formation of 2-methylcyclopentylamines by intramolecular hydroaminoalkylation of secondary 1-aminohex-5-enes.



Entry	Aminoalkene	Product	Yield [%][a]	Selectivity *trans*/*cis*[b]
1	 **7**	 **9**	84	34:66
2	 **29**	 **33**	73	37:63
3	 **30** OMe	 **34** OMe	86	32:68
4	 **31** F	 **35** F	85[c,d]	34:66
5	 **32** Cl	 **36** Cl	82	26:74

[a] *Reaction conditions:* aminoalkene (2.0 mmol), **11** (70 mg, 0.2 mmol, 10 mol%), *n*-hexane (2 mL), 140 °C, 96 h. Yields refer to the total yield of isolated product (*trans* + *cis*).
[b] GC analysis prior to chromatography.
[c] Under identical conditions, no conversion of **31** was observed with 10 mol% $Ti(NMe_2)_4$.
[d] An experiment performed with 20 mol% $Ta(NMe_2)_5$ gave a yield of 24% and a *trans*/*cis* ratio of 71:29.

cyclization experiments with secondary 1-aminohex-5-enes with a catalyst loading of 10 mol% and a reaction time of 96 h. The corresponding results which are presented in Table 3 clearly prove that **11** can also be used for intramolecular hydroaminoalkylation reactions (73–86%) of *N*-arylated secondary 1-aminohex-5-enes. The reaction tolerates electron-donating (CH_3, OCH_3) as well as electron-withdrawing substituents (F, Cl) on the phenyl group of the aminohexene and, in all cases, formation of the *cis*-diastereoisomer was clearly favored with *trans*/*cis* ratios in a range between approximately 1:2 and 1:3. The preferential formation of the *cis*-diastereoisomer has been observed before during the synthesis of cyclopentylamines from primary 1-aminohex-5-enes by hydroaminoalkylation performed with a 2-pyridonate titanium catalyst.[6j] In this context it should be noted that secondary *N*-methyl- or *N*-phenylaminoalkene substrates were unreactive with this catalyst.[6j] Although structure assignment of the *cis*- and *trans*-diastereoisomers of the cyclopentylamines could be achieved by ^{1}H NMR spectroscopy using NOE experiments, we additionally converted the major diastereoisomer of the *para*-fluoro-substituted product **35** (Table 3, entry 4) into

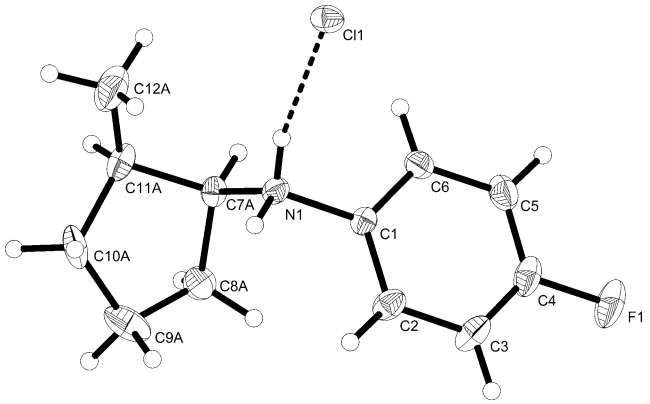


Figure 1. Single crystal X-ray structure of *cis*-**35·HCl**,[11] ellipsoid representation at the 50% probability level. Selected bond distances [Å] and angles [°]: N1–C1 = 1.4670(15), N1–C7A = 1.558(2), C7A–C8A = 1.524(3), C7A–C11A = 1.530(2), C8A–C9A = 1.517(3), C9A–C10A = 1.523(4), C10A–C11A = 1.553(4), C11A–C12A = 1.498(3), C7A–N1–C1 = 111.27(11), N1–C7A–C8A = 112.70(15), C7A–C8A–C9A = 105.96(16), C7A–C11A–C10A = 104.39(17), C8A–C9A–C10A = 105.97(18), C9A–C10A–C11A = 106.66(16), C12A–C11A–C7A = 117.59(17), C12A–C11A–C10A = 112.2(2).

the corresponding hydrochloride (*cis*-**35·HCl**) to obtain crystals suitable for X-ray single-crystal analysis. As can be seen from Figure 1, the solid state structure of *cis*-**35·HCl**[11] confirms the mentioned *cis*-1,2-disubstitution of the major diastereoisomer formed from 1-amino-5-hexene **31**.

To verify the outstanding catalytic activity of **11**, we additionally performed hydroaminoalkylation experiments with the fluoro-substituted 1-aminohex-5-ene **31** in the presence of $Ta(NMe_2)_5$ and $Ti(NMe_2)_4$. While the latter catalyst turned out to be completely inactive under the typical reaction conditions (140 °C, 96 h), an experiment performed with an increased catalyst loading of 20 mol% $Ta(NMe_2)_5$ led to the formation of product **35** in modest yield of 24% and with a *trans*/*cis* ratio of 71:29. The fact that, in comparison to catalyst **11**, the diastereoselectivity of the reaction is reversed suggests again that catalyst optimization should be an appropriate approach to control the diastereoselectivity of the intramolecular hydroaminoalkylation. Finally, it must be mentioned that attempts to achieve intramolecular hydroaminoalkylation of *N*-(oct-7-en-1-yl)-4-methoxyaniline to obtain the corresponding cycloheptylamine failed with catalyst **11**, even at temperatures of 200 °C.

Conclusions

In summary, our studies have shown that 2-aminopyridinato titanium complex **11** is an efficient catalyst for the intramolecular hydroaminoalkylation of secondary aminoalkenes. With this catalyst, various *N*-aryl-substituted 1-aminohept-6-enes and 1-aminohex-5-enes can be directly converted to 2-methylcyclohexyl- or 2-methylcyclopentylamines, which are common subunits of biologically active compounds, in good yields. In addition, it was possible for the first time, to achieve the metal-catalyzed intramolecular hydroaminoalkylation of an *N*-alkyl-substituted secondary aminoalkene as well as a geminally β-disubstituted substrate. While all products were formed as mixtures of a *trans*- and a *cis*-diastereoisomer, better diastereoselectivities with *trans*/*cis* ratios of approximately 1:3 were observed with 1-aminohex-5-enes which were converted to 2-methylcylopentylamines.

Experimental Section

General Remarks

Unless otherwise noted, all reactions were performed under an inert atmosphere of nitrogen in oven-dried Schlenk tubes (Duran glassware, 100 mL, ø = 30 mm) equipped with Teflon® stopcocks and magnetic stirring bars (15 × 4.5 mm). *n*-Hexane was purified by distillation from sodium wire and degassed. The catalyst **11**[6g,10] and the aminoalkenes[7,12] were synthesized according to literature procedures. Prior to use, all aminoalkenes were distilled and degassed. The catalyst, the aminoalkenes and *n*-hexane were stored in a nitrogen-filled glove box (M. Braun, Unilab). All other chemicals were purchased from commercial sources and were used without further purification. Unless otherwise noted, yields refer to isolated mixtures of two diastereoisomers (*trans* + *cis*). The ratio of the diastereoisomers formed during the reactions was usually determined by gas chromatography prior to flash chromatography. For thin layer chromatography, silica on TLC aluminium foils with fluorescent indicator 254 nm from Fluka was used. The substances were detected with UV light and/or iodine. For flash chromatography, silica gel from Fluka (particle size 0.037–0.063 mm) was used. Light petroleum ether (bp 40–60 °C, PE), ethyl acetate (EtOAc), hexanes, *tert*-butyl methyl ether (MTBE) and diethyl ether (Et_2O) used for flash chromatography were distilled prior to use. All products that have already been reported in the literature were identified by comparison of the obtained ^{1}H NMR and ^{13}C NMR spectra with those reported in the literature. New compounds were additionally characterized by infrared (IR) spectroscopy, GC-MS and high-resolution mass spectrometry (HR-MS). NMR spectra were recorded on the following spectrometers: Bruker Avance DRX 500 or Bruker Avance III, 500 MHz. All ^{1}H NMR spectra are reported in δ units (ppm) relative to the signal of TMS at 0.00 ppm or relative to the signal of $CDCl_3$ at 7.26 ppm or relative to the signal of D_2O at 4.79 ppm. *J* values are given in Hz. All ^{13}C NMR spectra are reported in δ units (ppm) relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm or the central line of the septet for DMSO-d_6 at 39.5 ppm. Infrared spectra were recorded on a Bruker Vector 22 spectrometer or a Bruker Tensor 27 spectrometer (ATR). GC-MS analyses were performed on a Thermo Finnigan Focus gas chromatograph equipped with

a DSQ mass detector and Agilent DB-5 column [length: 30 m, inner diameter: 0.32 mm, film thickness: 0.25 μm, (94%-methyl)-(5%-phenyl)-(1%-vinyl)polysiloxan]. GC analyses were performed on a Shimadzu GC-2010 plus or a Thermo Electron Corporation Focus gas chromatograph. Both were equipped with a flame ionization detector. High-resolution mass spectra (HR-MS) were recorded on a Waters Q-TOF Premier spectrometer in ESI mode (ESI+, TOF).

General Procedure for the Hydroaminoalkylation of Secondary Aminoalkenes

An oven-dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was transferred into a nitrogen-filled glovebox and charged with catalyst **11** (35 mg, 0.1 mmol, 5 mol% or 70 mg, 0.2 mmol, 10 mol%) and *n*-hexane (1.0 mL). Afterwards the aminoalkene (2.0 mmol) and *n*-hexane (1.0 mL) were added. After heating the mixture to 140 °C for 96 h, the mixture was cooled to room temperature and dichloromethane (40 mL) was added. Then the diastereoselectivity of the reaction was determined by GC (if applicable) and finally, the crude product was purified by flash column chromatography (SiO_2).

Amine 6:[4c] The general procedure was used to synthesize **6** from *N*-(hept-6-en-1-yl)aniline (**5**, 379 mg, 2.0 mmol). After purification by flash chromatography (PE/EtOAc, 30:1), a mixture of two diastereoisomers of **6** was isolated as a yellow oil; yield: 358 mg (1.89 mmol, 95%, 5 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 54:46. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the major diastereoisomer (*trans*-**6**)]: δ = 7.21–7.14 (m, 2H), 6.70–6.58 (m, 3H), 3.48 (br. s, 1H), 2.91 (td, J = 10.3, 3.8 Hz, 1H), 2.21–2.14 (m, 1H), 1.04 (d, J = 6.5 Hz, 3H); [important signals of the minor diastereoisomer (*cis*-**6**)]: δ = 7.21–7.14 (m, 2H), 6.70–6.58 (m, 3H), 3.57–3.51 (m, 1H), 3.48 (br. s, 1H), 2.08–1.99 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*trans*-**6**)]: δ = 148.2 (C), 129.2 (CH), 116.4 (CH), 112.8 (CH), 58.0 (CH), 39.2 (CH), 34.8 (CH_2), 33.5 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 19.6 (CH_3); [minor diastereoisomer (*cis*-**6**)]: δ = 147.7 (C), 129.2 (CH), 116.5 (CH), 113.1 (CH), 53.1 (CH), 33.1 (CH), 30.3 (CH_2), 28.7 (CH_2), 23.0 (CH_2), 22.8 (CH_2), 15.5 (CH_3).

Amine 10:[6b] The general procedure was used to synthesize **10** from *N*-(hept-6-en-1-yl)-4-methylaniline (**8**, 407 mg, 2.0 mmol). After purification by flash chromatography (PE/EtOAc, 40:1), a mixture of two diastereoisomers of **10** was isolated as a yellow oil; yield: 395 mg (1.94 mmol, 97%, 5 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 54:46. ^{1}H NMR [500 MHz, $CDCl_3$, TMS, mixture of two diastereoisomers; important signals of the major diastereoisomer (*trans*-**10**)]: δ = 6.99–6.92 (m, 2H), 6.49 (d, J = 8.3 Hz, 2H), 3.34 (br. s, 1H), 2.82 (td, J = 10.2, 3.6 Hz, 1H), 2.22 (s, 3H), 2.17–2.10 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H); [important signals of the minor diastereoisomer (*cis*-**10**)]: δ = 6.99–6.92 (m, 2H), 6.53 (d, J = 8.3 Hz, 2H), 3.48–3.43 (m, 1H), 3.34 (br. s, 1H), 2.04–1.95 (m, 1H), 0.91 (d, J = 7.0 Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*trans*-**10**)]: δ = 146.0 (C), 129.7 (CH), 125.6 (C), 113.0 (CH), 58.4 (CH), 39.2 (CH), 34.8 (CH_2), 33.6 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 20.3 (CH_3), 19.6 (CH_3); [minor diastereoisomer (*cis*-**10**)]: δ = 145.4 (C), 129.7 (CH), 125.7 (C), 113.3 (CH), 53.4 (CH), 33.1 (CH), 30.4 (CH_2), 28.6 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 20.3 (CH_3), 15.4 (CH_3).

Amine 22: The general procedure was used to synthesize **22** from *N*-(hept-6-en-1-yl)-3-methylaniline (**14**, 407 mg, 2.0 mmol). After purification by flash chromatography (PE/EtOAc, 50:1), a mixture of two diastereoisomers of **22** was isolated as a yellow oil; yield: 381 mg (1.88 mmol, 94%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 56:44. ^{1}H NMR [500 MHz, $CDCl_3$, TMS, mixture of two diastereoisomers; important signals of the major diastereoisomer (*trans*-**22**)]: δ = 7.07–6.92 (m, 1H), 6.50–6.27 (m, 3H), 3.46 (br. s, 1H), 2.86 (td, J = 10.2, 3.6 Hz, 1H), 2.26 (s, 3H), 2.17–2.10 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H); [important signals of the minor diastereoisomer (*cis*-**22**)]: δ = 7.07–6.92 (m, 1H), 6.50–6.27 (m, 3H), 3.53–3.45 (m, 1H), 3.46 (br. s, 1H), 2.26 (s, 3H), 2.05–1.93 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*trans*-**22**)]: δ = 148.1 (C), 138.9 (C), 129.1 (CH), 117.4 (CH), 113.6 (CH), 109.9 (CH), 58.0 (CH), 39.1 (CH), 34.8 (CH_2), 33.5 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 21.6 (CH_3), 19.6 (CH_3); [minor diastereoisomer (*cis*-**22**)]: δ = 147.7 (C), 138.9 (C), 129.1 (CH), 117.6 (CH), 113.9 (CH), 110.2 (CH), 53.1 (CH), 33.1 (CH), 30.3 (CH_2), 28.7 (CH_2), 23.0 (CH_2), 22.8 (CH_2), 21.6 (CH_3), 15.6 (CH_3); IR (neat, mixture of two diastereoisomers): $1/\lambda$ = 3402, 3042, 2924, 2853, 1603, 1510, 1489, 1447, 1325, 1263, 1178, 1116, 991, 842, 766, 692 cm^{-1}; GC-MS (major diastereoisomer, *trans*-**22**): m/z = 203 ($[M]^+$ 32), 146 (100), 120 (26), 91 ($[C_7H_7]^+$ 23); HR-MS (ESI+, mixture of two diastereoisomers): m/z = 204.1755, calcd. for $C_{14}H_{22}N$: 204.1752 ($[M+H]^+$).

Amine 23:[9] The general procedure was used to synthesize **23** from *N*-(hept-6-en-1-yl)-4-methoxyaniline (**15**, 439 mg, 2.0 mmol). After purification by flash chromatography (PE/Et_2O, 30:1), a mixture of two diastereoisomers of **23** was isolated as a yellow oil; yield: 355 mg (1.62 mmol, 81%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 27:73. ^{1}H NMR [500 MHz, $CDCl_3$, TMS, mixture of two diastereoisomers; important signals of the major diastereoisomer (*cis*-**23**)]: δ = 6.78–6.72 (m, 2H), 6.57 (d, J = 8.9 Hz, 2H), 3.73 (s, 3H), 3.42–3.37 (m, 1H), 2.04–1.96 (m, 1H), 0.91 (d, J = 7.0 Hz, 3H); [important signals of the minor diastereoisomer (*trans*-**23**)]: δ = 6.78–6.72 (m, 2H), 6.54 (d, J = 8.9 Hz, 2H), 3.73 (s, 3H), 2.76 (td, J = 10.2, 3.8 Hz, 1H), 2.18–2.09 (m, 1H), 1.01 (d, J = 6.5 Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*cis*-**23**)]: δ = 151.6 (C), 142.0 (C), 114.9 (CH), 114.6 (CH), 55.8 (CH_3), 54.3 (CH), 33.0 (CH), 30.5 (CH_2), 28.6 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 15.2 (CH_3); [minor diastereoisomer (*trans*-**23**)]: δ = 151.5 (C), 142.5 (C), 114.9 (CH), 114.3 (CH), 59.3 (CH), 55.9 (CH_3), 39.2 (CH), 34.8 (CH_2), 33.6 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 19.7 (CH_3).

Amine 24: The general procedure was used to synthesize **24** from 4-fluoro-*N*-(hept-6-en-1-yl)-aniline (**17**, 415 mg, 2.0 mmol). After purification by flash chromatography (PE/MTBE/Et_3N, 800:10:1), a mixture of two diastereoisomers of **24** was isolated as a yellow oil; yield: 160 mg (0.77 mmol, 39%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis*

ratio was determined to be 53:47. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the major diastereoisomer (*trans*-**24**)]: δ = 6.89–6.83 (m, 2H), 6.54–6.48 (m, 2H), 3.31 (br. s, 1H), 2.81 (td, J = 10.2, 3.8 Hz, 1H), 2.18–2.10 (m, 1H), 1.03 (d, J = 6.5 Hz, 3H); [important signals of the minor diastereoisomer (*cis*-**24**)]: δ = 6.93–6.87 (m, 2H), 6.58–6.52 (m, 2H), 3.47–3.40 (m, 1H), 3.31 (br. s, 1H), 2.07–1.98 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the major diastereoisomer (*trans*-**24**)]: δ = 59.0 (CH), 39.2 (CH), 34.8 (CH_2), 33.5 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 19.6 (CH_3); [important signals of the minor diastereoisomer (*cis*-**24**)]: δ = 54.0 (CH), 33.0 (CH), 30.4 (CH_2), 28.6 (CH_2), 22.9 (CH_2), 15.3 (CH_3); [additional signals]: δ = 155.3 (d, $^1J_{C,F}$ = 234.2 Hz, C), 155.3 (d, $^1J_{C,F}$ = 233.9 Hz, C), 144.6 (C), 144.1 (C), 115.6 (d, $^2J_{C,F}$ = 22.2 Hz, CH), 115.6 (d, $^2J_{C,F}$ = 22.2 Hz, CH), 114.0 (d, $^3J_{C,F}$ = 7.2 Hz, CH), 113.6 (d, $^3J_{C,F}$ = 7.2 Hz, CH); IR (neat, mixture of two diastereoisomers): $1/\lambda$ = 3424, 2926, 2855, 1612, 1509, 1448, 1404, 1311, 1257, 1220, 1155, 1117, 1092, 818, 763 cm^{-1}; GC-MS (major diastereoisomer, *trans*-**24**): m/z = 207 ([M]$^+$ 25), 150 (100), 124 (28), 95 (10); HR-MS (ESI+, mixture of two diastereoisomers): m/z = 208.1496, calcd. for $C_{13}H_{19}FN$: 208.1502 ([M+H]$^+$).

Amine 25: The general procedure was used to synthesize **25** from 4-chloro-*N*-(hept-6-en-1-yl)-aniline (**18**, 446 mg, 2.0 mmol). After purification by flash chromatography (PE/MTBE/Et_3N, 800:10:1), a mixture of two diastereoisomers of **25** was isolated as a yellow oil; yield: 230 mg (1.03 mmol, 52%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 51:49. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of *trans*-**25**]: δ = 3.54 (br. s, 1H), 2.87 (td, J = 10.3, 3.8 Hz, 1H), 2.19–2.11 (m, 1H), 1.05 (d, J = 6.5 Hz, 3H); [important signals of *cis*-**25**]: δ = 3.54 (br. s, 1H), 3.52–3.45 (m, 1H), 2.09–2.01 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of *trans*-**25**]: δ = 58.2 (CH), 39.1 (CH), 34.6 (CH_2), 33.3 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 19.5 (CH_3); [important signals of *cis*-**25**]: δ = 53.3 (CH), 33.0 (CH), 30.2 (CH_2), 28.5 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 15.4 (CH_3); [additional signals]: δ = 146.8 (C), 146.3 (C), 128.9 (CH), 128.8 (CH), 120.8 (C), 120.6 (C), 114.1 (CH), 113.7 (CH); IR (neat, mixture of two diastereoisomers): $1/\lambda$ = 3417, 2926, 2854, 1599, 1499, 1447, 1317, 1258, 1176, 1091, 813 cm^{-1}; GC-MS (major diastereoisomer, *trans*-**25**): m/z = 223 ([M]$^+$ 20), 166 (100), 130 (34), 75 ([C_6H_5]$^+$ 18); HR-MS (ESI+, mixture of two diastereoisomers): m/z = 224.1213, calcd. for $C_{13}H_{19}ClN$: 224.1206 ([M+H]$^+$).

Amine 26: The general procedure was used to synthesize **26** from *N*-(2-phenethyl)hept-6-enylamine (**21**, 435 mg, 2.0 mmol). The reaction was performed at 180 °C. After purification by flash chromatography (PE/MTBE/Et_3N, 50:10:1), a mixture of two diastereoisomers of **26** was isolated as a yellow oil; yield: 140 mg (0.6 mmol, 30%, 10 mol% **11**). After chromatography, the *trans*/*cis* ratio was determined by ^{1}H NMR to be approximately 1:1. ^{1}H NMR [500 MHz, $CDCl_3$, TMS, mixture of two diastereoisomers; important signals of *trans*-**26**]: δ = 1.94 (td, J = 10.1, 3.7 Hz, 1H), 0.76 (d, J = 6.5 Hz, 3H); [important signals of *cis*-**26**]: δ = 2.55–2.48 (m, 1H), 0.75 (d, J = 7.1 Hz, 3H); [additional signals]: δ = 7.24–7.16 (m, 4H), 7.15–7.08 (m, 6H), 2.95–2.82 (m, 1H), 2.63–2.28 (m, 7H), 1.90–1.79 (m, 2H), 1.67–1.05 (m, 14H), 1.01–0.85 (m, 2H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of *trans*-**26**]: δ = 62.9 (CH), 37.6 (CH), 34.5 (CH_2), 32.0 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 19.0 (CH_3); [important signals of *cis*-**26**]: δ = 58.4 (CH), 32.4 (CH), 31.0 (CH_2), 28.0 (CH_2), 23.8 (CH_2), 21.8 (CH_2), 13.3 (CH_3); [additional signals]: δ = 140.2 (C), 140.0 (C), 128.6 (CH), 128.3 (CH), 128.3 (CH), 126.0 (CH), 126.0 (CH), 48.4 (CH_2), 48.0 (CH_2), 36.5 (CH_2), 36.5 (CH_2); IR (neat, mixture of two diastereoisomers): $1/\lambda$ = 3027, 2925, 2853, 2360, 2341, 1671, 1633, 1602, 1495, 1454, 1376, 1126, 1082, 1030, 748 cm^{-1}; GC-MS (mixture of two diastereoisomers): m/z = 217 ([M]$^+$ 1), 126 (100), 97 (25); HR-MS (ESI+, mixture of two diastereoisomers): m/z = 218.1908, calcd. for $C_{15}H_{24}N$: 218.1909 ([M+H]$^+$).

Amine 28: The general procedure was used to synthesize **28** from *N*-(2,2-dimethylhept-6-en-1-yl)-4-methylaniline (**27**, 463 mg, 2.0 mmol). After purification by flash chromatography (PE/EtOAc, 100:1), three fractions of the diastereoisomers of **28** were isolated as pale yellow oils; yield: 70 mg (0.30 mmol, 15%, 10 mol% **11**). Fraction 1 contained the pure *cis*-diastereoisomer (*cis*-**28**); yield: 6 mg (0.03 mmol, 1%), fraction 2 contained a mixture of both diastereoisomers (*trans*/*cis* = 61:39); yield: 52 mg (0.22 mmol, 11%) and fraction 3 contained the pure *trans*-diastereoisomer (*trans*-**28**); yield: 12 mg (0.05 mmol, 3%). After chromatography, the *trans*/*cis* ratio of the combined fractions was determined by ^{1}H NMR to be approximately 63:37. Major diastereoisomer (*trans*-**28**): ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.94 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 3.20 (br. s, 1H), 2.67 (d, J = 10.6 Hz, 1H), 2.22 (s, 3H), 1.80–1.73 (m, 1H), 1.56–1.38 (m, 4H), 1.35–1.25 (m, 1H), 1.10–1.00 (m, 1H), 0.93 (s, 3H), 0.89 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.2 (C), 129.7 (CH), 124.8 (C), 112.3 (CH), 66.3 (CH), 40.9 (CH_2), 36.6 (C), 36.2 (CH), 35.6 (CH_2), 30.5 (CH_3), 21.6 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 19.5 (CH_3); IR (neat): $1/\lambda$ = 3413, 3015, 2945, 2921, 2866, 1617, 1518, 1456, 1316, 1281, 1250, 1181, 1097, 953, 803 cm^{-1}; GC-MS: m/z = 231 ([M]$^+$ 82), 160 (100), 120 ([C_8H_9N]$^+$ 41), 91 ([C_7H_7]$^+$ 7); HR-MS (ESI+): m/z = 232.2071, calcd. for $C_{16}H_{26}N$: 232.2065 ([M+H]$^+$). Minor diastereoisomer (*cis*-**28**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93 (d, J = 8.2 Hz, 2H), 6.53 (d, J = 8.3 Hz, 2H), 3.57 (br. s, 1H), 3.03 (d, J = 2.8 Hz, 1H), 2.21 (s, 3H), 2.09–2.00 (m, 1H), 1.56–1.50 (m, 2H), 1.47–1.40 (m, 1H), 1.37–1.28 (m, 1H), 1.23–1.16 (m, 1H), 1.13–1.01 (m, 1H), 1.05 (s, 3H), 0.89 (s, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.1 (C), 129.7 (CH), 124.9 (C), 112.6 (CH), 62.2 (CH), 36.2 (C), 33.7 (CH_2), 31.5 (CH), 29.1 (CH_3), 28.7 (CH_2), 25.8 (CH_3), 21.6 (CH_2), 20.3 (CH_3), 19.3 (CH_3); IR (neat): $1/\lambda$ = 3426, 3014, 2952, 2922, 2865, 1618, 1518, 1459, 1312, 1249, 1182, 1155, 1028, 802 cm^{-1}; GC-MS: m/z = 231 ([M]$^+$ 68), 160 (100), 120 ([C_8H_9N]$^+$ 43), 91 ([C_7H_7]$^+$ 8); HR-MS (ESI+): m/z = 232.2059, calcd. for $C_{16}H_{26}N$: 232.2065 ([M+H]$^+$).

Amine 9:[6b] The general procedure was used to synthesize **9** from *N*-(hex-5-en-1-yl)-4-methylaniline (**7**, 379 mg, 2.0 mmol). After purification by flash chromatography (PE/MTBE, 10:1), a mixture of two diastereoisomers of **9** was isolated as a pale yellow oil; yield: 318 mg (1.68 mmol, 84%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 34:66. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the

major diastereoisomer (*cis*-**9**)]: $\delta = 6.99$ (d, $J = 8.2$ Hz, 2H), 6.59–6.52 (m, 2H), 3.73 (q, $J = 6.7$ Hz, 1H), 2.33–2.27 (m, 1H), 2.25 (s, 3H), 0.90 (d, $J = 7.2$ Hz, 3H); [important signals of the minor diastereoisomer (*trans*-**9**)]: $\delta = 6.99$ (d, $J = 8.2$ Hz, 2H), 6.59–6.52 (m, 2H), 3.27 (q, $J = 6.7$ Hz, 1H), 2.25 (s, 3H), 2.20–2.10 (m, 1H), 1.09 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*cis*-**9**)]: $\delta = 145.9$ (C), 129.6 (CH), 125.8 (C), 113.1 (CH), 57.5 (CH), 35.7 (CH), 31.9 (CH_2), 31.4 (CH_2), 21.1 (CH_2), 20.3 (CH_3), 14.3 (CH_3); [minor diastereoisomer (*trans*-**9**)]: $\delta = 145.9$ (C), 129.6 (CH), 126.1 (C), 113.4 (CH), 62.0 (CH), 41.6 (CH), 32.8 (CH_2), 32.6 (CH_2), 22.5 (CH_2), 20.3 (CH_3), 18.9 (CH_3).

Amine 33:[13] The general procedure was used to synthesize **33** from *N*-(hex-5-en-1-yl)aniline (**29**, 351 mg, 2.0 mmol). After purification by flash chromatography (PE/MTBE, 40:1), a mixture of two diastereoisomers of **33** was isolated as a yellow oil; yield: 256 mg (1.46 mmol, 73%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 37:63. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the major diastereoisomer (*cis*-**33**)]: $\delta = 7.22$–7.15 (m, 2H), 6.72–6.66 (m, 1H), 6.66–6.59 (m, 2H), 3.76 (q, $J = 6.6$ Hz, 1H), 3.60 (br. s, 1H), 2.31 (sept, $J = 6.6$ Hz, 1H), 0.92 (d, $J = 7.0$ Hz, 3H); [important signals of the minor diastereoisomer (*trans*-**33**)]: $\delta = 7.22$–7.15 (m, 2H), 6.72–6.66 (m, 1H), 6.66–6.59 (m, 2H), 3.60 (br. s, 1H), 3.30 (q, $J = 6.7$ Hz, 1H), 2.23–2.13 (m, 1H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*cis*-**33**)]: $\delta = 148.1$ (C), 129.1 (CH), 116.6 (CH), 112.9 (CH), 57.2 (CH), 35.7 (CH), 31.9 (CH_2), 31.5 (CH_2), 21.2 (CH_2), 14.3 (CH_3); [minor diastereoisomer (*trans*-**33**)]: $\delta = 148.3$ (C), 129.1 (CH), 116.7 (CH), 113.0 (CH), 61.6 (CH), 41.7 (CH), 32.8 (CH_2), 32.6 (CH_2), 22.5 (CH_2), 18.9 (CH_3).

Amine 34: The general procedure was used to synthesize **34** from *N*-(hex-5-en-1-yl)-4-methoxyaniline (**30**, 411 mg, 2.0 mmol). After purification by flash chromatography (PE/MTBE, 10:1), a mixture of two diastereoisomers of **34** was isolated as a yellow oil; yield: 354 mg (1.72 mmol, 86%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 32:68. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the major diastereoisomer (*cis*-**34**)]: $\delta = 6.81$–6.74 (m, 2H), 6.62–6.55 (m, 2H), 3.75 (s, 3H), 3.68 (q, $J = 6.8$ Hz, 1H), 2.27 (sept, $J = 6.8$ Hz, 1H), 0.89 (d, $J = 7.1$ Hz, 3H); [important signals of the minor diastereoisomer (*trans*-**34**)]: $\delta = 6.81$–6.74 (m, 2H), 6.62–6.55 (m, 2H), 3.75 (s, 3H), 3.23–3.18 (m, 1H), 2.16–2.07 (m, 1H), 1.08 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*cis*-**34**)]: $\delta = 151.6$ (C), 142.4 (C), 114.8 (CH), 114.2 (CH), 58.0 (CH), 55.8 (CH_3), 35.6 (CH), 31.9 (CH_2), 31.4 (CH_2), 21.1 (CH_2), 14.2 (CH_3); [minor diastereoisomer (*trans*-**34**)]: $\delta = 151.8$ (C), 142.6 (C), 114.8 (CH), 114.4 (CH), 62.6 (CH), 55.8 (CH_3), 41.6 (CH), 32.9 (CH_2), 32.6 (CH_2), 22.5 (CH_2), 19.0 (CH_3); IR (neat, mixture of two diastereoisomers): $1/\lambda = 3398$, 2954, 2869, 1731, 1618, 1512, 1462, 1408, 1377, 1235, 1179, 1111, 1040, 818, 757 cm^{-1}; GC-MS (major diastereoisomer, *cis*-**34**): $m/z = 205$ ($[M]^+$ 60), 162 (100), 108 (37), 77 ($[C_6H_5]^+$ 16); HR-MS (ESI+, mixture of two diastereoisomers): $m/z = 206.1550$, calcd. for $C_{13}H_{20}NO$: 206.1536 ($[M+H]^+$).

Amine 35: The general procedure was used to synthesize **35** from 4-fluoro-*N*-(hex-5-en-1-yl)aniline (**31**, 387 mg, 2.0 mmol). The amount of added dichloromethane during the work-up procedure was 20 mL. After purification by flash chromatography (PE/MTBE, 30:1), two fractions of the diastereoisomers of **35** were isolated as colorless to pale yellow oils; yield: 329 mg (1.70 mmol, 85%, 10 mol% **11**). Fraction 1 contained the pure *cis*-diastereoisomer (*cis*-**35**) and fraction 2 contained a mixture of both diastereoisomers (*trans*/*cis* = 83:17). Prior to chromatography, the *trans*/*cis* ratio was determined to be 34:66. Isolation of pure *trans*-**35** could be achieved by column chromatography of fraction 2 using a Büchi Sepacore® Flash System X10 (Büchi Plastiglas® column, 36 × 460 mm; solvent: PE/MTBE; program: 3 min 0% MTBE, 30 min +1% MTBE/min; flow rate: 90 mL min^{-1}; 0–30 atm). Major diastereoisomer (*cis*-**35**): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.90$–6.83 (m, 2H), 6.57–6.51 (m, 2H), 3.68 (q, $J = 6.7$ Hz, 1H), 3.52 (br. s, 1H), 2.27 (sept, $J = 6.8$ Hz, 1H), 2.04–1.94 (m, 1H), 1.92–1.82 (m, 1H), 1.79–1.67 (m, 1H), 1.64–1.47 (m, 2H), 1.45–1.36 (m, 1H), 0.89 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.4$ (d, $^1J_{C,F} = 234.2$ Hz, C), 144.6 (C), 115.5 (d, $^2J_{C,F} = 22.3$ Hz, CH), 113.6 (d, $^3J_{C,F} = 7.4$ Hz, CH), 57.9 (CH), 35.7 (CH), 32.0 (CH_2), 31.5 (CH_2), 21.2 (CH_2), 14.3 (CH_3); IR (neat): $1/\lambda = 3425$, 3058, 3036, 2958, 2871, 1613, 1509, 1456, 1312, 1220, 1155, 1101, 818, 773 cm^{-1}; GC-MS: $m/z = 193$ ($[M]^+$ 30), 150 (100), 111 (20); HR-MS (ESI+): $m/z = 194.1342$, calcd. for $C_{12}H_{17}FN$: 194.1345 ($[M+H]^+$). Minor diastereoisomer (*trans*-**35**): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.90$–6.83 (m, 2H), 6.57–6.51 (m, 2H), 3.48 (br. s, 1H), 3.21 (q, $J = 6.6$ Hz, 1H), 2.18–2.10 (m, 1H), 1.97–1.87 (m, 1H), 1.82–1.65 (m, 3H), 1.45–1.35 (m, 1H), 1.27 (dq, $J = 12.7$, 8.3 Hz, 1H), 1.09 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.5$ (d, $^1J_{C,F} = 234.4$ Hz, C), 144.7 (C), 115.5 (d, $^2J_{C,F} = 22.3$ Hz, CH), 113.8 (d, $^3J_{C,F} = 7.4$ Hz, CH), 62.2 (CH), 41.6 (CH), 32.7 (CH_2), 32.6 (CH_2), 22.5 (CH_2), 18.9 (CH_3); IR (neat): $1/\lambda = 3405$, 3073, 3056, 3039, 2953, 2900, 2868, 1846, 1609, 1504, 1451, 1405, 1375, 1317, 1294, 1201, 1155, 1115, 1103, 991, 920, 851, 815, 801, 765 cm^{-1}; GC-MS: $m/z = 193$ ($[M]^+$ 31), 164 (12), 150 (100), 137 (16), 124 (11), 111 (10), 95 (8); HR-MS (ESI+): $m/z = 194.1347$, calcd. for $C_{12}H_{17}FN$: 194.1345 ($[M+H]^+$).

Amine hydrochloride (*cis*-35·HCl): Under an atmosphere of argon, an oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with dry diethyl ether (2 mL) and *cis*-**35** (238 mg, 1.23 mmol). The resulting solution was cooled to −10 °C while a solution of hydrogen chloride in diethyl ether (0.6 mL, 2 M, 1.23 mmol) was added dropwise. After the resulting suspension had been stirred for additional ten minutes at −10 °C, the suspension was filtered and the solid material was washed with dry diethyl ether (3 × 2 mL). After evaporation of the solvent, hydrochloride *cis*-**35·HCl** was obtained as a colorless solid; yield: 220 mg (0.96 mmol, 78%). ^{1}H NMR (500 MHz, D_2O): $\delta = 7.53$–7.47 (m, 2H), 7.33–7.26 (m, 2H), 3.91 (q, $J = 7.0$ Hz, 1H), 2.40 (sept, $J = 7.0$ Hz, 1H), 1.94–1.77 (m, 3H), 1.76–1.67 (m, 1H), 1.65–1.54 (m, 1H), 1.52–1.45 (m, 1H), 1.11 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, D_2O, DMSO-d_6): $\delta = 164.0$ (d, $^1J_{C,F} = 247.5$ Hz, C), 132.0 (d, $^4J_{C,F} = 2.9$ Hz, C), 126.7 (d, $^3J_{C,F} = 9.2$ Hz, CH), 118.7 (d, $^2J_{C,F} = 23.6$ Hz, CH), 68.7 (CH), 36.6 (CH), 32.5 (CH_2), 28.1 (CH_2), 22.0 (CH_2), 15.0 (CH_3); IR (neat): $1/\lambda = 2965$, 2879, 2658, 2576, 2513, 2447, 1609, 1508,

1454, 1427, 1236, 1196, 1160, 1099, 1017, 840, 760 cm^{-1}; HRMS (ESI+): $m/z = 194.1341$, calcd. for $C_{12}H_{17}NF$ (ammonium ion): 194.1345 ($[M]^+$). Colorless crystals suitable for X-ray single-crystal analysis[11] were obtained by storing a test tube filled with a saturated solution of *cis*-**35·HCl** in toluene for three days at room temperature in a closed 500 mL Erlenmeyer flask which was charged with light petroleum ether (20 mL).

Amine 36: The general procedure was used to synthesize **36** from 4-chloro-*N*-(hex-5-en-1-yl)aniline (**32**, 419 mg, 2.0 mmol). After purification by flash chromatography (PE/MTBE, 10:1), a mixture of two diastereoisomers of **36** was isolated as a yellow oil; yield: 344 mg (1.64 mmol, 82%, 10 mol% **11**). Prior to chromatography, the *trans*/*cis* ratio was determined to be 26:74. ^{1}H NMR [500 MHz, $CDCl_3$, mixture of two diastereoisomers; important signals of the major diastereoisomer (*cis*-**36**)]: $\delta = 7.12–7.07$ (m, 2H), 6.56–6.48 (m, 2H), 3.69 (q, $J = 6.7$ Hz, 1H), 3.66 (br. s, 1H), 2.27 (sept, $J = 6.9$ Hz, 1H), 0.88 (d, $J = 7.1$ Hz, 3H); [important signals of the minor diastereoisomer (*trans*-**36**)]: $\delta = 7.12–7.07$ (m, 2H), 6.56–6.48 (m, 2H), 3.23 (q, $J = 6.9$ Hz, 1H), 2.18–2.09 (m, 1H), 1.07 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR [125 MHz, $CDCl_3$, mixture of two diastereoisomers; major diastereoisomer (*cis*-**36**)]: $\delta = 146.8$ (C), 129.0 (CH), 121.2 (C), 114.0 (CH), 57.4 (CH), 35.7 (CH), 32.0 (CH_2), 31.5 (CH_2), 21.2 (CH_2), 14.3 (CH_3); [minor diastereoisomer (*trans*-**36**)]: $\delta = 146.9$ (C), 129.0 (CH), 121.2 (C), 114.2 (CH), 61.9 (CH), 41.7 (CH), 32.7 (CH_2), 32.6 (CH_2), 22.5 (CH_2), 18.9 (CH_3); IR (neat, mixture of two diastereoisomers): $1/\lambda = 3420$, 2957, 2870, 1600, 1499, 1456, 1318, 1249, 1176, 1089, 814 cm^{-1}; GC-MS (major isomer *cis*-**36**): $m/z = 209$ ($[M]^+$ 37), 166 (100), 154 (30), 140 (62), 111 (21); HR-MS (ESI+, mixture of two diastereoisomers): $m/z = 210.1042$, calcd. for $C_{12}H_{17}ClN$: 210.1050 ($[M+H]^+$).

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[11] Single crystal X-ray data of *cis*-**35·HCl** (colorless crystal, dimensions $0.24 \times 0.14 \times 0.08$ mm^3) were measured on a Bruker AXS Apex II diffractometer (Mo-Kα radi-

ation, $\lambda = 0.71073$ Å, Kappa 4 circle goniometer, Bruker Apex II detector). An absorption correction based on symmetry-related measurements (multi-scan) was performed with the program SADABS (G. M. Sheldrick, University of Göttingen, Germany, 2014); the structure was solved with the program SHELXS and refined with SHELXL-2014/7 (G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3–8). The 2-methylcyclopentane unit is disordered over 3 sites with refined occupancies of 73%, 18%, and 9%. Non H atoms of the major site were refined anisotropically, atoms belonging to the minor sites were refined isotropically, and their geometries restrained to that of the major site (using the SAME instruction within the SHELXL program); amine H atoms were refined freely, other H atoms were fixed to geometric positions using the riding model. Crystal data: formula $C_{12}H_{17}ClFN$, $M = 229.71$, orthorhombic space group *Pccn*, $a = 17.2353(5)$ Å, $b = 18.8292(5)$ Å, $c = 7.3825(2)$ Å, $V = 2395.82(11)$ Å^3, $Z = 8$, $\rho = 1.274$ mg cm^{-3}, $\mu = 0.300$ mm^{-1}, $\theta_{max} = 30.034°$, $T = 100(2)$ K, 51502 reflections measured, 3514 unique [$R_{int} = 0.0398$], 2965 observed [$I > 2\sigma(I)$], 186 parameters refined using 40 restraints, $R_1 = 0.0375$, $wR_2 = 0.0920$ for the observed reflections, and $R_1 = 0.0469$, $wR_2 = 0.0976$ for all data, largest difference peaks 0.567 and −0.293 e Å^{-3}. CCDC 1042824 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[12] For experimental details, see the Supporting Information.

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